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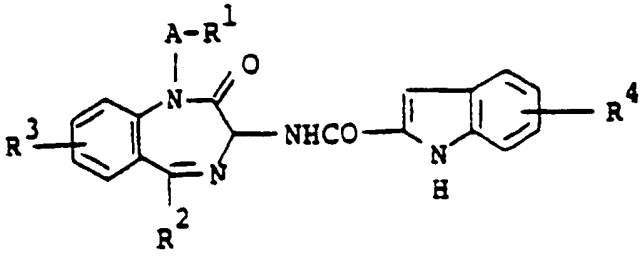
(54) Benzodiazepine derivatives.

(57) A compound of the formula :



wherein R^1 is halogen,
heterocyclic group which may have one or more suitable substituent(s), aryl which may have one or more suitable substituent(s),
-NH-R^5 (in which R^5 is hydrogen, lower alkanoyl or hydroxy(lower)alkyl),
-S-R^6 (in which R^6 is lower alkyl, lower alkyl substituted with carboxy and amino, lower alkyl substituted with protected carboxy and protected amino, or pyridyl),
-O-R^7 (in which R^7 is hydrogen, hydroxy protective group, lower alkyl, lower alkenyl, ar(lower)alkyl, halo-(lower)alkyl, amino(loweralkyl, protected amino(lower)alkyl, or piperazinyl(lower)alkyl which may have lower alkyl),
-CONH-R^8 (in which R^8 is cyano, carbamoyl(lower)alkyl, carboxy(lower)alkyl, protected carboxy(lower)alkyl, or lower alkyl substituted with carbamoyl and aryl), or
-Z-R^9 [in which R^9 is hydrogen or lower alkyl, and Z is

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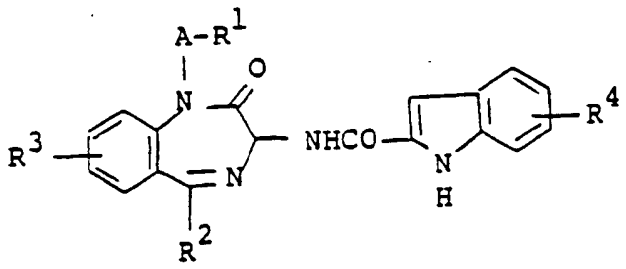
BENZODIAZEPINE DERIVATIVES

This invention relates to new benzodiazepine derivatives and pharmaceutically acceptable salts thereof.

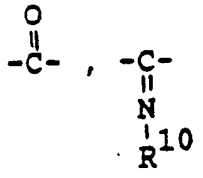
More particularly, it relates to new benzodiazepine derivatives and pharmaceutically acceptable salts thereof which are cholecystokinin (CCK) antagonists and therefore can be used as therapeutical agents for emesis, pancreatitis, satiety and appetite control, pain control, insulinoma, gastroparesis, acute obstructive cholecystitis, irritable bowel disease, carcinoma of pancreas, etc.

The benzodiazepine derivatives of this invention can be represented by the following formula (I) :

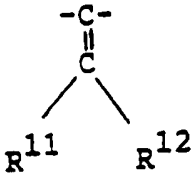


(I)

wherein R^1 is halogen,
heterocyclic group which may have one or more suitable substituent(s),
aryl which may have one or more suitable substituent(s),
-NH-R^5 (in which R^5 is hydrogen, lower alkanoyl or hydroxy(lower)alkyl,
-S-R^6 (in which R^6 is lower alkyl, lower alkyl substituted with carboxy and amino, lower alkyl substituted with protected carboxy and protected amino, or pyridyl),
-O-R^7 (in which R^7 is hydrogen, hydroxy protective group, lower alkyl, lower alkenyl, ar(lower)alkyl, halo(lower)alkyl, amino(lower)alkyl, protected amino(lower)alkyl, or piperazinyl(lower)alkyl which may have lower alkyl),
-CONH-R^8 (in which R^8 is cyano, carbamoyl(lower)alkyl, carboxy(lower)alkyl, protected carboxy(lower)alkyl, or lower alkyl substituted with carbamoyl and aryl), or
-Z-R^9 [in which R^9 is hydrogen or lower alkyl, and Z is

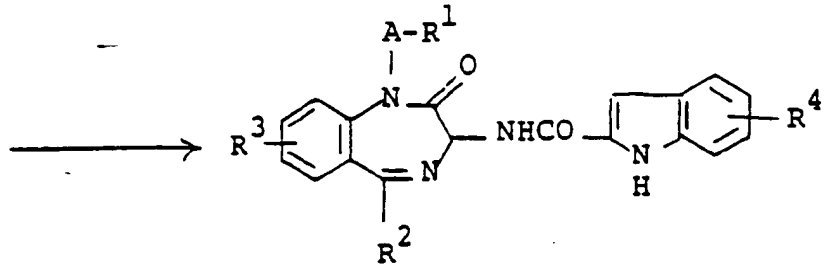


(wherein R^{10} is hydroxy, lower alkoxy or amino or



(wherein R^{11} is carboxy or protected carboxy and R^{12} is hydrogen; or R^{11} is halogen and R^{12} is halogen)],
R^2 is aryl which may have one or more suitable substituent(s),
R^3 is hydrogen or halogen,
R^4 is hydrogen, halogen or lower alkoxy and
A is lower alkylene.

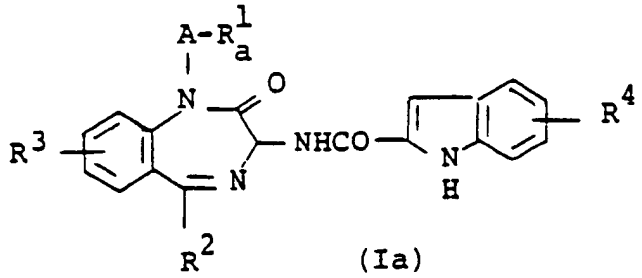
According to the present invention, the new benzodiazepine derivatives (I) can be prepared by the processes which are illustrated in the following scheme.



(I)

or a salt thereof

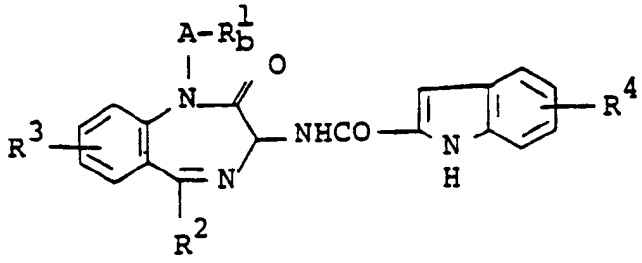
Process 3



(Ia)

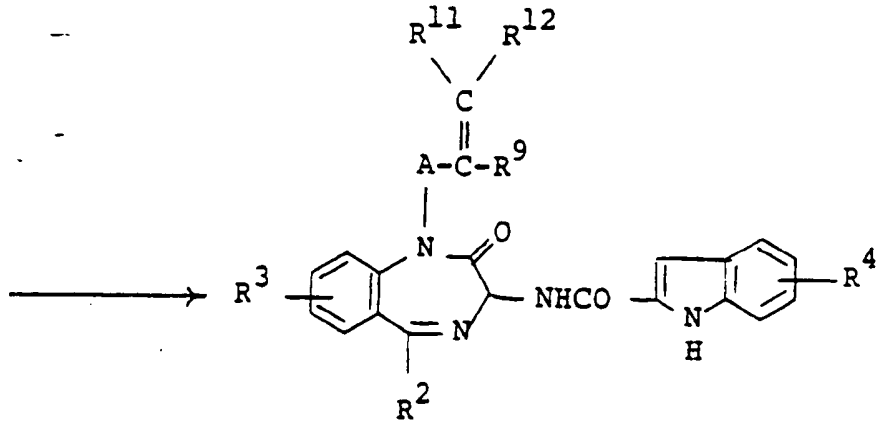
or a salt thereof

Elimination reaction of the hydroxy protective group



(Ib)

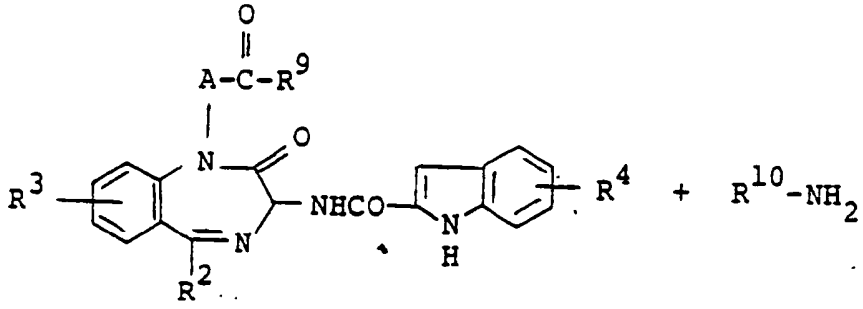
or a salt thereof



(If)

or a salt thereof

Process 6

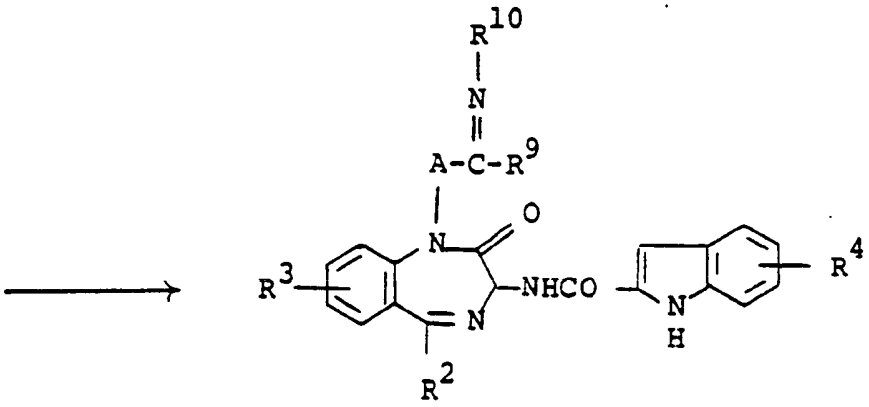


(Ie)

or a salt thereof

(XI)

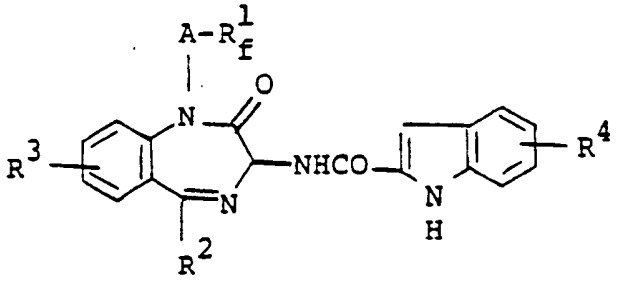
or a salt thereof



(Ig)

or a salt thereof

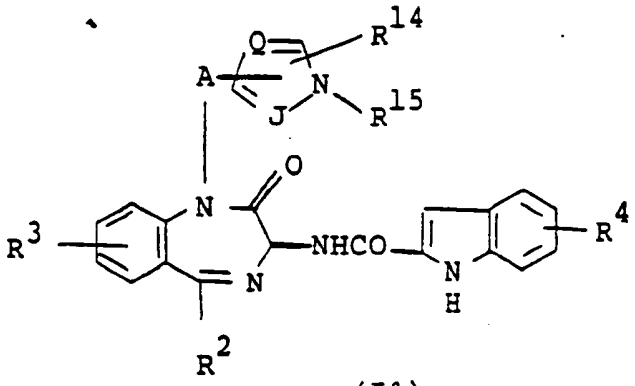
Elimination reaction of the carboxy protective group



(Ik)

or a salt thereof

Process 9

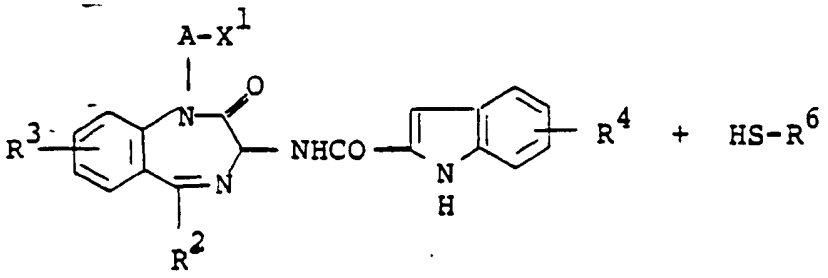


(Iℓ)

or a salt thereof

Elimination reaction of the imino protective group

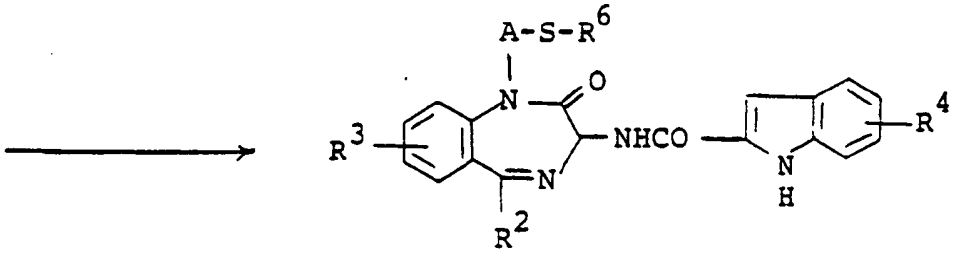
Process 11



(Io)
or a salt thereof

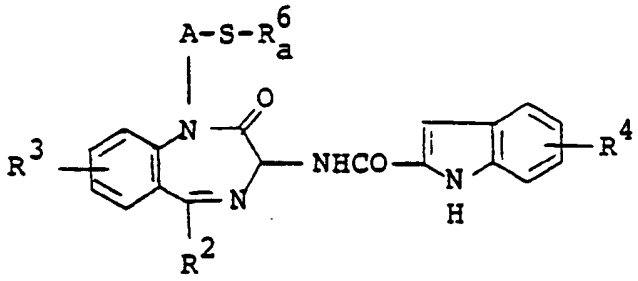
+ HS-R^6

(XIV)
or a salt thereof



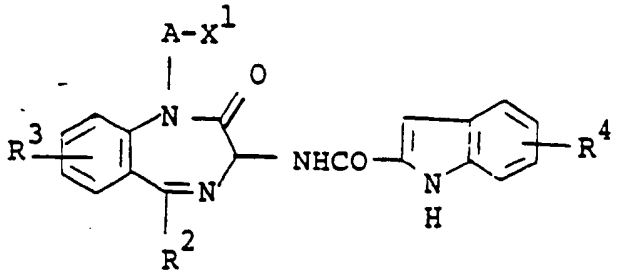
(Ip)
or a salt thereof

Process 12



(Iq)
or a salt thereof

Process 14

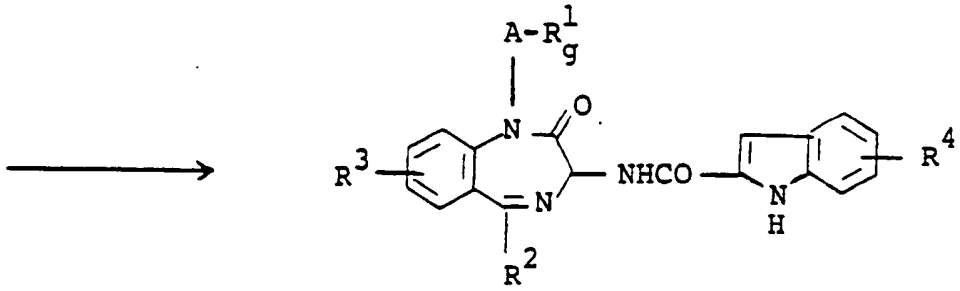


(Io)

or a salt thereof

(XVI)

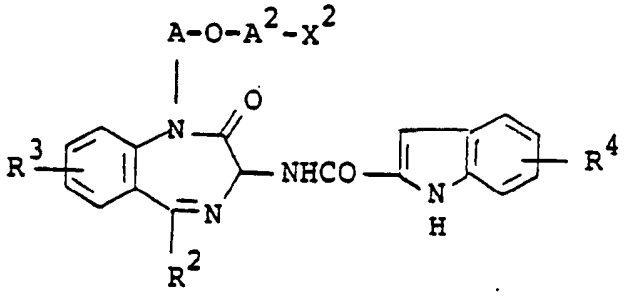
or a salt thereof



(Iu)

or a salt thereof

Process 15



(Iv)

or a salt thereof

(XVII)

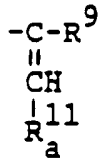
or a salt thereof

R^{13} is aryl,

R^1_c is heterocyclic group having protected amino, phthalimido, or -O-R^7_b (in which R^7_b is protected amino-(lower)alkyl),

R^1_d is heterocyclic group having amino, amino,or -O-R^7_c (in which R^7_c is amino(lower)alkyl),

R^1_e is



(in which R^9 is as defined above, R^{11}_a is a protected carboxy group) or -CONH-R^8_a (in which R^8_a is protected carboxy(lower)alkyl),

R^1_f is

(in which R^9 is as defined above) or -CONH-R^8_b (in which R^8_b is carboxy(lower)alkyl),

R^{14} is hydrogen or lower alkyl,

R^{15} is an imino protective group,

J is CH or N,

Q is CH or N,

X^1 is halogen,

R^6_a is lower alkyl substituted with protected carboxy and protected amino,

R^6_b is lower alkyl substituted with carboxy and amino,

R^5_a is lower alkanoyl,

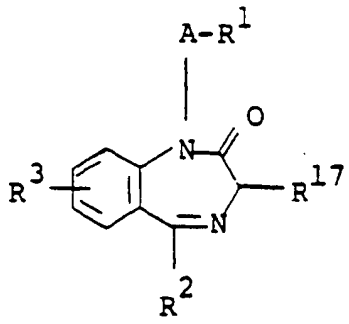
R^1_g is piperazinyl having lower alkyl, or _NH-R^5 (in which R^5 is as defined above),

X^2 is halogen,

A^2 is lower alkylene, and

R^{16} is phthalimido or piperazinyl having lower alkyl.

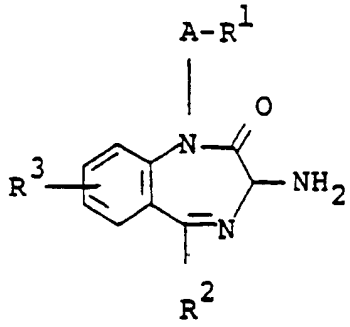
The starting compound (IV) is novel and can be prepared by the following processes.



(IX)

or a salt thereof

(3) Elimination reaction of the amino protective group



(IV)

or a salt thereof

wherein
R^1, R^2, R^3, A and X are each as defined above,
Y is an acid residue, and
R^{17} is a protected amino group.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N′-dibenzylethylenediamine salt, etc.), an organic acid salt (e.g. acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable "halogen" and "halogen moiety" in the term "halo(lower)alkyl" may include chlorine, bromine, fluorine and iodine.

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like. And, especially preferably heterocyclic group may be heterocyclic group such as unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example,

mesityl ester, cumenyl ester, etc.]; or the like.

Suitable "protected amino" and "protected amino moiety" in the term "protected amino(lower)alkyl" may include an acylamino or an amino group substituted by a conventional protective group such as ar-(lower)alkyl which may have at least one suitable substituent(s), (e.g. benzyl, trityl, etc.) or the like.

Suitable acyl moiety in the terms "acylamino" and "acyloxy" may include aliphatic acyl group and acyl group containing an aromatic or heterocyclic ring.

And, suitable examples of the said acyl may be lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.);
lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 1-cyclopropylethoxycarbonyl, isopropovycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.);
lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, etc.);
arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.); aroyl (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl, indancarbonyl, etc.);
ar(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, etc.);
ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), and the like.

The acyl moiety as stated above may have at least one suitable substituent(s) such as halogen (chlorine, bromine, fluorine and iodine), amino, lower alkoxycarbonylamino (e.g. methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, isopropoxycarbonylamino, butoxycarbonylamino, tert-butoxycarbonylamino, pentyloxycarbonylamino, hevyloxycarbonylamino, etc.) or the like.

Suitable "hydrovy protective group" may include tetrahydropyranyl, acyl group such as lower alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, etc.), and the like.

Suitable "lower alkenyl" may include vinyl, allyl, 1-propenyl, 1 or 2 or 3-butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl and the like.

Suitable "lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like, preferably one having 1 to 4 carbon atom(s).

Suitable "lower alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene or the like, preferably one having 1 to 4 carbon atoms(s).

Suitable "imino protective group" may include trityl, tetrahydropyranyl and thelike.

Suitable "acid residue" may include acyloxy wherein acyl moiety is as mentioned above, halogen (e.g., fluorine, chlorine, bromine and iodine) and the like.

The preferred embodiments of the object compound (I) are as follows.

Preferred embodiment of

R^1 is halogen,
thienyl,
furyl,
piperazinyl having lower alkyl,
imidazolyl which may have trityl,
imidazolyl having lower alkyl,
imidazolyl having trityl and lower alkyl,
pyrazolyl which may have trityl,
triazolyl which may have trityl,
thiazolyl having amino or protected amino (more preferably thiazolyl having amino or acylamino, most preferably thiazolyl having amino or lower alkanoylamino),
isoxazolyl having hydroxy,
dihydroisoxazolyl having oxo and
tetrahydropyranyl,
tetrazolyl,
isoindolyl having two oxo groups,
phenyl,
phenyl having two protected hydroxy groups (more preferably phenyl having two acyloxy groups, most preferably phenyl having two lower alkanoyloxy groups),
phenyl having two hydroxy groups,
phenyl having two lower alkoxy groups,
$-NH-R^5$ (in which R^5 is hydrogen, lower alkanoyl or hydroxy(lower)alkyl),
$-S-R^6$ [in which R^6 is lower alkyl, lower alkyl substituted with carboxy and amino, lower alkyl substituted with protected carboxy and protected amino (more preferably lower alkyl substituted with esterified carboxy and acylamino, most preferably lower alkyl substituted with diphenyl(lower)alkoxycarbonyl and lower

Process 1 :

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof.

Suitable salts of the compounds (II) and (III) can be referred to the ones as exemplified for the compound (I).

This reaction is usually carried out in the presence of base.

Suitable base may include an inorganic base such as alkali metal hydride (e.g. sodium hydride, etc.) alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like, and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine or the like.

This reaction is usually carried out in a solvent such as alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 2 :

The compound (I) or a salt thereof can be prepared by reacting the compound (IV) or its reactive derivative at the amino group or a salt thereof with the compound (V) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the amino group of the compound (IV) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (IV) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (IV) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (IV) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (IV) and (V) can be referred to the ones as exemplified for the compound (I).

Suitable reactive derivative at the carboxy group of the compound (V) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. The suitable example may be an acid chloride, an acid azide; a mixed acid anhydride with an acid such as s" diluted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g. methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2\overset{+}{N}=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with a N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.), and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (V) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

When the compound (V) is used in free acid form or its salt form in the reaction, the reaction is

affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 5 :

The compound (If) or a salt thereof can be prepared by reacting the compound (Ie) or a salt thereof with the compound (X) or a salt thereof.

Suitable salts of the compounds (Ie) and (If) can be referred to the ones as exemplified for the compound (I).

This reaction is usually carried out in a solvent such as benzene, N,N-dimethylformamide, tetrahydrofuran, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 6 :

The compound (Ig) or a salt thereof can be prepared by reacting the compound (Ie) or a salt thereof with the compound (XI) or a salt thereof.

Suitable salts of the compound (Ig) can be referred to the ones as exemplified for the compound (I).

This reaction is usually carried out in a solvent such as benzene, N,N-dimethylformamide, tetrahydrofuran, alcohol (e.g., methanol, ethanol, etc.), chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 7

The compound (Ii) or a salt thereof can be prepared by subjecting the compound (Ih) or a salt thereof to elimination reaction of the amino protective group.

This reaction is carried out by substantially the same method as that of Process A - ③, and therefore the reaction method and conditions can be referred to said Process A - ③ .

Process 8

The compound (Ik) or a salt thereof can be prepared by subjecting the compound (Ij) or a salt thereof to elimination reaction of the carboxy protective group.

This reaction is carried out by substantially the same method as that of Process 3, and therefore the reaction method and conditions can be referred to said Process 3.

Process 9

The compound (Im) or a salt thereof can be prepared by subjecting the compound (Il) or a salt thereof to elimination reaction of the imino protective group.

This reaction carried out by substantially the same method as that of Process A - ③ , and therefore the reaction method and condition can be referred to said Process A - ③ .

Process 10

The compound (In) or a salt thereof can be prepared by reacting the compound (XII) or its reactive derivative at the carboxy group or a salt thereof with the compound (XIII) or its reactive derivative at the amino group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (XII) can be referred to the ones as exemplified for the compound (V).

Suitable reactive derivative at the amino group of the compound (XIII) can be referred to the ones as

The compound (Iy) or a salt thereof can be prepared by subjecting the compound (Ix) or a salt thereof to elimination reaction of the imino protective group.

This reaction is carried out by substantially the same method as that of Process 9, and therefore the reaction method and conditions can be referred to said Process 9.

The processes for preparing the starting compound (IV) are explained in the following.

Process A - ① :

The compound (VIII) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with the compound (VII) or a salt thereof. The reaction method and conditions can be referred to those of Preparation 1 as mentioned below.

Process A - ② :

The compound (IX) or a salt thereof can be prepared by reacting the compound (VIII) or a salt thereof with the compound (III) or a salt thereof. This reaction is carried out by substantially the same method as that of Process 1, and therefore the reaction method and conditions are to be referred to said Process 1.

Process A - ③ :

The compound (IV) or a salt thereof can be prepared by subjecting the compound (IX) or a salt thereof to elimination reaction of the amino protective group.

Suitable salts of the compound (IX) can be referred to the ones as exemplified for the compound (I).

The elimination reaction is carried out in accordance with a conventional method such as hydrolysis; reduction; Edman's method (phenyl isothiocyanate method); or the like. The hydrolysis may include a method using an acid or base or hydrazine and the like. These methods may be selected depending on the kind of the protective groups to be eliminated.

Among these methods, hydrolysis using an acid is one of the most common .and preferable method for eliminating the protective groups such as substituted or unsubstituted alkoxycarbonyl, for example, tert-pentyloxycarbonyl, lower alkanoyl (e.g. formyl, acetyl, etc.), cycloalkoxycarbonyl, substituted or unsubstituted aralkoxycarbonyl, aralkyl (e.g. trityl), substituted phenylthio, substituted aralkylidene, substituted alkylidene, substituted cycloalky-lidene or the like. Suitable acid includes an organic or inorganic acid such as formic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, hydrochloric acid and the like, and the most suitable acid is an acid which can easily be removed from the reaction mixture by a conventional manner such as distillation under reduced pressure, for example, formic acid, trifluoroacetic acid, hydrochloric acid, etc. The acids can be selected according to the kind of the protective group to be eliminated.

The elimination reaction using trifluoroacetic acid may be carried out in the presence of anisole. The hydrolysis using hydrazine is commonly applied for eliminating a phthaloyl, succinyl type amino-protective group.

The elimination using base is used for eliminating an acyl group such as trifluoroacetyl. Suitable base may include an inorganic base and an organic base.

The reductive elimination is generally applied for eliminating the protective group, for example, haloalkoxycarbonyl (e.g. trichloroethoxycarbonyl, etc.), substituted or unsubstituted aralkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), 2-pyridylmethoxycarbonyl, etc. Suitable reduction may include, for example, reduction with an alkali metal borohydride (e.g. sodium borohydride, etc.), reduction with a combination of a metal (e.g. tin, zinc, iron, etc.) or the said metal together with a metal salt compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, etc.); and catalytic reduction. Suitable catalyst includes a conventional one, for example, Raney nickel, platinum oxide, palladium on carbon and the like.

Among the protective groups, the acyl group can generally be eliminated by hydrolysis. Especially, halogen substituted-alkoxycarbonyl and 8-quinolyloxycarbonyl groups are usually eliminated by treating with a heavy metal such as copper, zinc, or the like.

The reaction is usually carried out in a conventional solvent such as water, chloroform, methylene chloride, alcohol (e.g., methanol, ethanol, etc.), tetrahydrofuran or any other organic solvent which does not

Preparation 1

A mixture of (3RS)-1,3-dihydro-3-acetoxy-5-phenyl2H-1,4-benzodiazepine-2-one (11.75 g), potassium phthalimide (11.1 g), sodium iodide (60 g) and N,N-dimethylformamide (80 ml) was stirred for 45 minutes at 90 to 95°C. The reaction mixture was poured into a cold water (1 ℓ). The precipitates were collected by filtration, washed with water and recrystallized from ethanol to give (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-2H-1,4-benzodiazepine-2-one (8.32 g).
IR (Nujol) : 3500, 3370, 3230, 1780, 1720, 1695, 1610, 1575 cm^{-1}
NMR (DMSO-d_6, δ) : 5.73 (1H, s), 7.30-7.70 (9H, m), 7.97 (4H, m), 11.90 (1H, br s)

Preparation 2

A mixture of (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-2H-1,4-benzodiazepine-2-one (8.2 g), hydrazine hydrate (1.08 g) and tetrahydrofuran (160 ml) was stirred for 1.0 hour at room temperature and heated under reflux for 1.5 hours. After the precipitates were filtered off, the filtrate was evaporated to small volume and the equivalent volume of diisopropyl ether was added thereto. The precipitates were collected by filtration to give (3RS)-1,3-dihydro-3-amino-5-phenyl-2H-1,4-benzodiazepine-2-one (3.64 g).
IR (Nujol) : 3360, 3290, 2700, 1670, 1600, 1570, 1480 cm^{-1}
NMR (DMSO-d_6, δ) : 4.30 (1H, s), 5.0 (2H, br s), 7.20-7.60 (9H, m)

Preparation 3

To a solution of (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-2H-1,4-benzodiazepine-2-one (1.90 g) in N,N-dimethylformamide (30 ml) was added sodium hydride (62% suspension in mineral oil; 0.20 g) gradually with stirring under cooling in an ice-bath (<3°C). The mixture was stirred for 10 minutes under the same conditions. To the resultant mixture was added 2-[(tetrahydropyran-2-yl)oxy]ethyl bromide (1.60 g) in one portion. The mixture was stirred at ambient temperature for one hour and at 45°C for 4.5 hours and allowed to stand overnight. The resultant reaction mixture was poured into water and extracted with ethyl acetate twice. The extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave light yellow powder, which was washed with a mixture of ethyl acetate and diethyl ether and collected by filtration to afford a mixture (1.48 g) of (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-1-.{2-((RS)-2-tetrahydropyranyloxy) ethyl} 2H-1,4-benzodiazepine-2-one and (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-1-{2-((SR)-2-tetrahydropyranyloxy)ethyl} 2H-1,4-benzodiazepine-2-one.
IR (Nujol) : 1770, 1714, 1670, 1600, 1375, 1130, 1014, 710 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-1.9 (6H, broad), 3.4-4.7 (7H, m), 6.00 (1H, s), 7.3-8.1 (13H, m)

Preparation 4

To a solution of a mixture (0.51 g) of (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-1-{2-((RS)-2-tetrahydropyranyloxy)ethyl}-2H-1,4-benzodiazepine-2-one and (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-1-{2-((SR)-2-tetrahydropyranyloxy)ethyl}-2H-1,4-benzodiazepine-2-one in chloroform (10 ml) was added hydrazine hydrate (55 mg) at ambient temperature under stirring. The mixture was stirred for 1.5 hours under the same conditions and heated under reflux for 1.5 hours. After cooling, the resultant precipitate was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in a small amount of ethanol and diethyl ether was added thereto. White powder was filtered off again and the filtrate was evaporated to give a crude mixture (0.43 g) of (3RS)-1,3-dihydro-5-phenyl-3-amino-1-{2-((RS)-2-tetrahydropyranyloxy)ethyl}-2H-1,4-benzodiazepine-2-one and (3RS)-1,3-dihydro-5-phenyl-3-amino-1-{2-(-(SR)-2-tetrahydropyranyloxy)ethyl}-2H-1,4-benzodiazepine-2-one.
IR (Nujol) : 3340, 1680, 1660, 1600, 780, 760, 695 cm^{-1}

Example 1

To a solution of (3RS)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (1.18 g) in N,N-dimethylformamide (30 ml) was added sodium hydride (62% suspension in mineral oil; 0.26

(1) To a solution of a mixture (1.0 g) of (3R)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one and (3S)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one in N,N-dimethylformamide (5 ml) was added sodium hydride (77.4 mg, 62% suspension in mineral oil) under stirring with cooling in an ice-bath (ca. 3° C). The mixture was stirred for 40 minutes under the same condition. To the resultant mixture was added 2-acetoxyethyl bromide (0.37 g) at once under stirring and cooling. The mixture was stirred for 1.5 hours under ice-cooling and for 2 hours at ambient temperature. The reaction mixture was poured into water and extracted with ethyl acetate twice. The extracts were combined, washed with brine and dried over magnesium sulfate. Removal of the solvent by evaporation gave an oil (1.29 g), which was subjected to column chromatography on silica gel with an eluent of a mixture of chloroform and ethyl acetate (10:1). The fractions containing the desired compound were combined and evaporated to afford a colorless oily mixture (0.84 g) of (3R)-1-(2-acetoxyethyl)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one and (3S)-1-(2-acetoxyethyl)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one.

IR (liquid) : 3400 (shoulder), 3300, 1730, 1700 (shoulder), 1690, 1660, 1600, 745, 695 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 (9H, s), 1.62 (3H, s), 3.0-3.3 (2H, m), 3.9-4.2 (3H, m), 4.4-4.8 (2H, m), 5.06 (1H, broad d), 5.51 & 5.53 (1H, d & d), 7.2-7.85 (14H, m)

The following compound was obtained according to a similar manner to that of Preparation 5(1).

(2) Mixture of (3R)-1-(2-acetoxyethyl)-1,3-dihydro-5-(2-fluorophenyl)-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one and (3S)-1-(2-acetoxyethyl)-1,3-dihydro-5-(2-fluorophenyl)-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one

IR (liquid) : 3400 (shoulder), 3320, 1730, 1700 (shoulder), 1690, 1662, 1485, 1440, 1380, 1365, 1230, 1161, 1048, 750, 695 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 (9H, s), 1.79 (3H, s), 3.0-3.3 (2H, m), 3.8-4.8 (5H, m), 5.07 (1H, broad d, J = 7.4Hz), 5.53, 5.55 (1H, dd, J = 8Hz), 6.95-7.9 (14H, m)

Preparation 6

To a solution of a mixture (0.7 g) of (3R)-1-(2-acetoxyethyl)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one and (3S)-1-(2-acetoxyethyl)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one in ethyl acetate (20 ml) was introduced hydrogen chloride gas under cooling in an ice-bath with stirring. After the solution was saturated with hydrogen chloride, the mixture was stirred for 30 minutes under the same temperature and for 1 hour at ambient temperature. After removal of the hydrogen chloride by bubbling dried nitrogen gas, the mixture was evaporated under reduced pressure. To the residue was added water and the mixture was neutralized with a saturated aqueous solution of sodium bicarbonate. The mixture was extracted with ethyl acetate twice and the extract was washed with water and dried over magnesium sulfate. Removal of the solvent afforded a mixture (0.57 g) of (3R)-1-(2-acetoxyethyl)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one and (3S)-1-(2-acetoxyethyl)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one.

Preparation 7

A mixture (12.2 g) of (3R)-1-(2-acetoxyethyl)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one (3R-isomer) and (3S)-1-(2-acetoxyethyl)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one (3S-isomer) was subjected to a column chromatography on silica gel (230-400 mesh) with an eluent of a mixture of chloroform and methanol (20:1). The fractions containing the object compound were combined and evaporated to dryness to give pure 3S-isomer (3.32 g) as an oil. From the other fractions, an oily mixture (8.50 g) of 3S-isomer and 3R-isomer was obtained. The oily mixture was re-chromatographed on silica gel (230-400 mesh) with an eluent of a mixture of chloroform and methanol (15:1) to give an oily pure 3S-isomer (1.30 g) and an oily pure 3R-isomer (4.01 g).

NMR ($CDCl_3$ + D_2O, δ) 270 MHz :

3S-isomer

1.648 (3H, s), 2.817 (1H, dd, J = 14.0Hz, 10.8Hz), 3.336 (1H, dd, J = 14Hz, 6.5Hz), 3.704 (1H, dd, J = 10.8Hz,

IR (Film) : 3450 (sh), 3380, 3325 (sh), 1738, 1680, 1660 (sh), 1605, 1580, 1490, 1455, 1375, 1332, 1230, 1110, 1050, 820, 760, 745 cm^{-1}
NMR ($CDCl_3$, δ) : 1.81 (3H, s), 3.8-4.8 (6H, m), 6.95-7.9 (9H, m)
$[\alpha]_D^{25}$: -57.68° (3.10 mg/ml, CH_2Cl_2)

(4) (3R)-1-(2-Acetoxyethyl)-3-amino-1,3-dihydro-5-fluorophenyl)-2H-1,4-benzodiazepine-2-one

IR (Film) : 3450 (sh), 3350, 3325 (sh), 1736, 1690 (sh), 1673, 1650 (sh), 1600, 1580, 1482, 1450, 1370, 1328, 1222, 1105, 1000, 815, 750 cm^{-1}
NMR ($CDCl_3$, δ) : 1.80 (3H, s), 3.8-4.8 (6H, m), 6.95-7.9 (9H, m)
$[\alpha]_D^{25}$: 50.52° (3.18 mg/ml, CH_2Cl_2)

Example 4

(1) To a solution of (3S)-1-(2-acetoxyethyl)-3-amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one g) in N,N-dimethylformamide (25 ml) were added indole-2-carboxylic acid (0.64 g), N-hydroxybenzotriazole (0.54 g) and N,N'-dicyclohexylcarbodiimide (0.83 g) under stirring at ambient temperature. The mixture was stirred for 2 hours at the same temperature and allowed to stand overnight. The resultant precipitates were filtered off and the filtrate and the washings were combined. The solvent (N,N-dimethylformamide) was evaporated under reduced pressure. To the residue was added water and the mixture was extracted with ethyl acetate. The extract was washed with brine twice and dried over magnesium sulfate. Removal of the solvent afforded an oil (3.05 g), which was subjected to column chromatography on silica gel with an eluent of a mixture of chloroform and methanol (15:1). The fractions containing the desired product were combined and evaporated under reduced pressure to give (3S)-1-(2-acetoxyethyl)-3-(2-indolylcarbonylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one (1.90 g).
IR (Nujol) : 3325, 3260, 1735, 1680, 1630, 1600, 1230, 745, 697 cm^{-1}
NMR ($CDCl_3$, δ) : 1.65 (3H, s), 3.8-4.3 (3H, m), 4.55-4.9 (1H, m), 5.84 (1H, d, J = 8.25Hz), 7.0-7.8 (14H, m), 8.14 (1H, d, J = 8.25Hz), 9.98 (1H, br s)
MASS : m/e = 481(M^+)
$[\alpha]_D^{26.8}$: -51.27° (0.00340 g/ml, $CHCl_3$)
The following compounds were obtained according to a similar manner to that of Example 4(1).

(2) (3R)-1-(2-Acetoxyethyl)-3-(2-indolylcarbonylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one.

IR (Nujol) : 3325, 3260, 1735, 1680, 1630, 1600, 1230, 745, 697 cm^{-1}
NMR ($CDCl_3$, δ) : 1.65 (3H, s), 3.8-4.3 (3H, m), 4.55-4.9 (1H, m), 5.84 (1H, d, J = 8.25Hz) 7.0-7.8 (14H, m), 8.14 (1H, d, J = 8.25Hz), 10.06 (1H, br s)
MASS : m/e = 481 (M^+)
$[\alpha]_D^{26.8}$: 58.90° (0.00300 g/ml, $CHCl_3$)

(3) (3S)-1-(2-Acetoxyethyl)-3-(2-indolylcarbonylamino)-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

mp : 183-187° C (dec.)
IR (Nujol) : 3350 (sh), 3275, 1733, 1687, 1640, 1610 (sh), 1539, 1455, 1380, 1260, 1235, 821, 775, 750 cm^{-1}
NMR ($CDCl_3$, δ) : 1.80 (3H, s), 3.8-4.25 (3H, m), 4.45-4.85 (1H, m), 5.84 (1H, d, J = 8Hz), 6.9-7.9 (13H, m), 8.15 (1H, d, J = 8Hz), 10.11 (1H, broad s)
MASS : m/e = 498 (M^+)

(4) (3R)-1-(2-Acetoxyethyl)-3-(2-indolylcarbonylamino)-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

mp : 185-189° C (dec.)
IR (Nujol) : 3325 (sh), 3260, 1726, 1682, 1635, 1610 (sh), 1535, 1448, 1372, 1255, 1226, 820, 770, 745 cm^{-1}
NMR ($CDCl_3$, δ) : 1.81 (3H, s), 3.8-4.3 (3H, m), 4.55-4.85 (1H, m), 5.84 (1H, d, J = 8Hz), 6.9-7.85 (13H, m), 8.14 (1H, d, J = 8Hz), 10.00 (1H, broad s)
MASS : m/e = 498 (M^+)

chloroform as an eluent to give the pure product of (3RS)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-1-(2-methoxyethyl)-2H-1,4-benzodiazepine-2-one (110 mg).
mp : 180-185° C (dec.)
IR (Nujol) : 3440, 3275, 1685, 1630, 1600, 1540, 1490 cm^{-1}
NMR ($CDCl_3$, δ) : 3.13 (3H, s), 3.45-3.65 (2H, m), 3.80-4.50 (2H, m), 5.80 (1H, d, J = 8Hz), 7.0-7.80 (14H, m), 8.15 (1H, d, J = 8Hz), 9.75 (1H, s)

The following compound was obtained according to a similar manner to that of Example 6(1).

(2) (3RS)-1-Acetylmethyl-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one

IR (Nujol) : 3325, 3250, 1720, 1680, 1630, 1530, 1448, 1375, 740, 695 cm^{-1}
NMR (DMSO-d_6, δ) : 2.16 (3H, s), 4.71 (2H, s), 5.90 (1H, d, J = 7.5Hz), 7.0-7.75 (14H, m), 8.09 (1H, d, J = 7.5Hz), 10.01 (1H, broad s)
MASS : m/e = 450 (M^+)

Example 7

(3RS)-1,3-Dihydro-1-(2-hydroxyethyl)-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (0.30 g) was dissolved in a mixture of anhydrous dimethylsulfoxide (1 ml) and benzene (1 ml) containing pyridine (0.056 ml) and trifluoroacetic acid (0.028 ml). After addition of dicyclohexylcarbodiimide (0.42 g), the mixture was stirred overnight at room temperature. Water was added thereto and the insoluble dicyclohexylurea was removed by filtration. The filtrate was extracted with ethyl acetate twice and the organic layer was washed with water, aqueous sodium bicarbonate and water respectively. The extract was dried over magnesium sulfate and evaporated to give an amorphous oil (0.53 g), which was subjected to column chromatography on silica gel with a mixture of chloroform and ethyl acetate (5:1) as an eluent. The fractions containing the objective materials were combined and evaporated to afford white powder, which was purified by washing with diisopropyl ether to give pure (3RS)-1,3-dihydro-1-formylmethyl-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (0.20 g).
mp : 168° C (dec.)
IR (Nujol) : 3400 (shoulder), 3270, 1725, 1680, 1635, 1600, 1445, 1375, 745, 695 cm^{-1}
NMR ($CDCl_3$, δ) : 4.68 (2H, s), 5.90 (1H, d, J = 7.5Hz), 7.0-7.75 (14H, m), 8.07 (1H, d, J = 7.5Hz), 9.66 (1H, s), 10.05 (1H, broad s)
MASS : m/e = 436 (M^+)

Example 8

To a solution of (3RS)-1,3-dihydro-1-formylmethyl-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (0.44 g) in chloroform (10 ml) was added methoxycarbonylmethylenetriphenylphosphorane (0.37 g). The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to give a residual oil, which was subjected to column chromatography on silica gel with a mixture of chloroform and ethyl acetate (10:1) as an eluent.

(3RS)-1,3-dihydro-1-[(Z)-3-methoxycarbonyl-2- propenyl)-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (64.6 mg) was obtained from the former fractions.
IR (Nujol) : 3340, 3250, 1718, 1700, 1665, 1637, 1598, 1536, 1450, 1375, 805, 740, 690 cm^{-1}
NMR ($CDCl_3$, δ) : 3.74 (3H, s), 5.24 (2H, dd, J = 6Hz, 1.5Hz), 5.86 (1H, d, J = 8Hz), 5.90 (1H, dt, J = 12.7Hz, 1.5Hz), 6.21 (1H, dt, J = 12.7Hz, 6Hz), 7.1-7.8 (14H, m), 8.13 (1H, d, J = 8Hz), 9.98 (1H, broad s)

(3RS)-1,3-dihydro-1-[(E)-3-methoxycarbonyl-2-propenyl)-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (291.1 mg) was obtained from the later fractions.
IR (Nujol) : 3340, 3270, 1711, 1685, 1635, 1600, 1535, 1450, 1375, 830, 772, 740, 700 cm^{-1}
NMR ($CDCl_3$, δ) : 3.64 (3H, s), 4.7-4.82 (2H, m), 5.87 (1H, d, J = 7.5Hz), 5.88 (1H, dt, J = 16.5Hz, 1.5Hz), 6.94 (1H, dt, J = 16.5Hz, 4.5Hz), 7.1-7.8 (14H, m), 8.11 (1H, d, J = 7.5Hz), 9.92 (1H, broad s)

Example 9

A mixture of (3RS)-1-acetylmethyl-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-

benzodiazepine-2-one

mp : 205-210° C (dec.)
NMR (DMSO-d_6, δ) : 1.96 (3H, s), 4.80, 5.15 (2H, ABq, J = 15Hz), 5.55 (1H, d, J = 8Hz), 6.90-8.15 (15H, m), 9.33 (1H, d, J = 8Hz), 11.58 (2H, br s)
MASS : m/e = 488 (M^+)

(4) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(2-imidazolylmethyl)-5-phenyl-2H-1,4-benzodiazepine-2-one

mp : 175-180° C (dec.)
NMR (DMSO-d_6, δ) : 5.10 (2H, s), 5.65 (1H, d, J = 8Hz), 6.60-8.10 (16H, m), 9.36 (1H, d, J = 8Hz), 11.65 (1H, br s), 11.90 (1H, br s)
MASS : m/e = 474 (M^+)

(5) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(3-pyrazolylmethyl)-5-phenyl-2H-1,4-benzodiazepine-2-one

mp : 255-260° C (dec.)
NMR (DMSO-d_6, δ) : 5.03, 5.30 (2H, ABq, J = 15Hz), 5.65 (1H, d, J = 8Hz), 5.85 (1H, br s), 6.90-7.90 (15H, m), 9.43 (1H, d, J = 8Hz), 11.60 (1H, br s), 12.55 (1H, br s),
MASS : m/e = 474 (M^+)

(6) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-[(1,2,4-triazol-3-yl)methyl]-5-phenyl-2H-1,4-benzodiazepine-2-one

mp : 205-210° C (dec.)
NMR (DMSO-d_6, δ) : 5.10, 5.35 (2H, ABq, J = 15Hz), 5.66 (1H, d, J = 8Hz), 6.90-7.93 (15H, m), 8.23 (1H, br s), 9.40 (1H, d, J = 8Hz), 11.65 (1H, br s)
MASS : m/e = 475 (M^+)

(7) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-[2-(4-imidazolyl)ethyl]-5-phenyl-2H-1,4-benzodiazepine-2-one

mp : 185-190° C (dec.)
NMR (DMSO-d_6, δ) : 2.63 (2H, t, J = 7Hz), 3.85-4.20 (1H, m), 4.20-4.75 (1H, m), 5.55 (1H, d, J = 8Hz), 6.60 (1H, s), 6.93-7.85 (15H, m), 9.43 (1H, d, J = 8Hz), 11.65 (1H, br s)
MASS : m/e = 488 (M^+)

Example 12

The following compound was obtained according to a similar manner to that of Example 5(1).

(3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(2-hydroxyethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

IR (Nujol) : 3240, 1670, 1630, 1530 cm^{-1}
NMR (DMSO-d_6, δ) : 3.30-3.90 (2H, m), 3.90-4.40 (1H, m), 4.70-5.0 (1H, m), 5.70 (1H, d, J = 8Hz), 6.90-8.0 (13H, m), 9.50 (1H, d, J = 8Hz), 11.50 (1H, br s)
MASS : m/e = 456(M^+)

Example 13

The following compounds were obtained according to a similar manner to that of Example 6(1).

(1) (3RS)-1-(2-Acetoxyethyl)-1,3-dihydro-5-(2-fluorophenyl)-3-(2-indolylcarbonylamino)-2H-1,4-

mp : 175-180° C (dec.)
NMR ($CDCl_3$, δ) : 1.93 (3H, s), 4.83, 5.30 (2H, ABq, J = 15Hz), 5.85 (1H, d, J = 8Hz), 6.53 (1H, s), 6.90-7.70 (14H, m), 8.25 (1H, d, J = 8Hz), 9.56 (1H, s), 10.0 (1H, s)

(10) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(2-bromoethyl)-5-phenyl-2H-1,4-benzodiazepine-2-one

NMR ($CDCl_3$, δ) : 3.30-3.70 (2H, m), 3.85-4.40 (1H, m), 4.60-5.20 (1H, m), 5.83 (1H, d, J = 8Hz), 7.0-7.90 (14H, m), 8.15 (1H, d, J = 8Hz), 10.05 (1H, s)

(11) (3RS)-1,3-Dihydro-1-[[2-(2-tetrahydropyranyl)-3-oxo-2,3-dihydroisoxazol-5-yl]methyl]-3-(2-indolylcarbonylamino)-5-phenyl-1,4-benzodiazepine-2-one

IR (Nujol) : 3260, 1700, 1682, 1630 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-2 (6H, m), 3.5-4.2 (2H, m), 4.8-5.6 (4H, ABq), 5.89 (1H, d, J = 8Hz), 7.1-7.9 (14H, m), 8.04 (1H, d, J = 8Hz), 9.7 (1H, br s)

(12) (3RS)-1,3-Dihydro-3-[(5-chloroindol-2-yl)carbonylamino]-5-phenyl-1-(2-methoxyethyl)-2H-1,4-benzodiazepine-2-one

mp : >260° C
IR (Nujol) : 3350 (sh), 3290, 1668, 1630, 1596, 1530, 1445, 1374, 1324, 1240, 1215, 1110, 910, 759, 690 cm^{-1}
NMR ($CDCl_3$, δ) : 3.10 (3H, s), 3.45-3.75 (2H, m), 3.80-4.53 (2H, m), 5.77 (1H, d, J = 8.0Hz), 6.9-7.7 (13H, m), 8.12 (1H, d, J = 8.0Hz), 10.26 (1H, br s)
MASS : m/e = 487 (M^+)

(13) (3RS)-1,3-Dihydro-3-[(5-methoxyindol-2-yl)carbonylamino]-5-phenyl-1-(2-methoxyethyl)-2H-1,4-benzodiazepine-2-one

mp : 221-222° C
IR (Nujol) : 3400 (sh), 3250, 1673, 1630, 1596, 1530, 1447, 1375, 1322, 1235, 1115, 1024, 842, 802, 762, 694 cm^{-1}
NMR ($CDCl_3$, δ) : 3.11 (3H, s), 3.45-3.75 (2H, m), 3.82 (3H, s), 3.80-4.55 (2H, m), 5.78 (1H, d, J = 8.0Hz), 6.75-7.7 (13H, m), 8.04 (1H, d, J = 8.0Hz), 9.90 (1H, br s)
MASS : m/e = 482 (M^+)

(14) (3RS)-1-(3-Bromopropyl)-3-(2-indolylcarbonylamino)-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one

IR (Nujol) : 3400 (sh), 3250, 1675, 1633, 1600, 1530, 1445, 1375, 1242, 800, 742, 692 cm^{-1}
NMR ($CDCl_3$, δ) : 1.8-2.3 (2H, m), 2.95-3.4 (2H, m), 3.8-4.75 (1H, dt, J = 13.8Hz, 6.6Hz), 4.35-4.65 (1H, dt, J = 13.8Hz, 6.6Hz), 5.77 (1H, d, J = 8Hz), 7.0-7.7 (14H, m), 8.15 (1H, d, J = 8Hz), 9.97 (1H, br s)

Example 14

A mixture of (3RS)-1,3-dihydro-3-(2-indolylcarbonylamino)-1-[(2-acetamidothiazol-4-yl)methyl]-5-phenyl-2H-1,4-benzodiazepine-2-one, methanol (13 ml), tetrahydrofuran ml) and conc. hydrochloric acid (0.8 ml) was stirred for 7.0 hours at 70° C, cooled and adjusted to pH 7.0 with % aqueous solution of sodium bicarbonate. To the mixture were added water (100 ml) and ethyl acetate (100 ml) under cooling. The separated organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel with an eluent of a mixture of ethyl acetate and chloroform (2:1) to give (3RS)-1,3-dihydro-3-(2-indolylcarbonylamino)-1-[(2-aminothiazol-4-yl)methyl]-5-phenyl-2H-1,4-benzodiazepine-2-one.
mp : 200-205° C (dec.)
NMR (DMSO-d_6, δ) : 4.80, 5.06 (2H, ABq, J = 15Hz), 5.60 (1H, d, J = 8Hz), 6.06 (1H, s), 6.75 (2H, br s), 6.90-7.95 (14H, m), 9.40 (1H, d, J = 8Hz), 11.65 (1H, s)
MASS : m/e = 506 (M^+)

Example 18

To a suspension of (3RS)-1,3-dihydro-1-[[2-(2-tetrahydropyranyl)-3-oxo-2,3-dihydroisoxazol-5-yl]methyl]-3-(2-indolylcarbonylamino)-5-phenyl-1,4-benzodiazepine-2-one (212.9 mg) in methanol (4 ml) was added 2N hydrochloric acid under stirring at room temperature. Tetrahydrofuran (1 ml) was added thereto in order to gain a clear solution, which was stirred at the same temperature for 30 minutes. The reaction mixture was evaporated to dryness to afford yellow powder, which was washed with ether by stirring overnight, collected by filtration and dried to give (3RS)-1,3-dihydro-1-[(3-hydroxyisoxazol-5-yl)methyl]-3-(2-indolylcarbonylamino)-5-phenyl-1,4-benzodiazepine-2-one (149.1 mg) as yellow powder.
mp : 207° C (dec.)
NMR (DMSO-d_6, δ) : 5.24 (2H, ABq, J = 15Hz, 25.5Hz), 5.67 (1H, d, J = 8Hz), 5.70 (1H, s), 7.0-7.85 (14H, m), 9.52 (1H, d, J = 8Hz), 11.61 (1H, broad s)
MASS : m/e = 491 (M^+)

Example 19

The following compounds were obtained according to a similar manner to that of Example 6(1).

(1) (3RS)-1-[2-(2-Chloroethovy)ethyl]-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one

NMR ($CDCl_3$, δ) : 3.20-4.60 (8H, m), 5.80 (1H, d, J = 8Hz), 7.0-7.80 (14H, m), 8.15 (1H, d, J = 8Hz), 10.20 (1H, br s)

(2) (3RS)-1-(2-Vinyloxyethyl)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one

mp : 210-215° C (dec.)
NMR ($CDCl_3$, δ) : 3.75-4.0 (4H, m), 4.0-4.20 (1H, m), 4.30-4.65 (1H, m), 5.76 (1H, d, J = 8Hz), 6.05-6.35 (1H, m), 7.0-7.75 (14H, m), 8.03 (1H, d, J = 8Hz), 9.53 (1H, br s)
MASS : m/e = 464 (M^+)

(3) (3RS)-1-(2-Benzyloxyethyl)-1,3-dihydro-3-(2-indolylcarbonylamino-5-phenyl-2H-1,4-benzodiazepine-2-one

mp : 195-200° C (dec.)
NMR ($CDCl_3$, δ) : 3.55-3.80 (2H, m), 3.80-4.20 (1H, m), 4.20-4.55 (1H, m), 4.30 (2H, s), 5.75 (1H, d, J = 8Hz), 6.96-7.80 (14H, m), 8.06 (1H, d, J = 8Hz), 9.85 (1H, br s)

(4) (3RS)-1-(3,4-Dimethoxybenzy,-1,3-dihydro-3-(2-indolylcarbonylamino-5-phenyl-2H-1,4-benzodiazepine-2-one

mp : 220-225° C (dec.)
IR (Nujol) : 3300, 3200, 1680, 1635, 1590, 1525, 1505 cm^{-1}
NMR ($CDCl_3$, δ) : 3.40 (3H, s), 3.75 (3H, s), 4.70, 5.75 (2H, ABq, J = 15Hz), 5.90 (1H, d, J = 8Hz), 6.45-6.65 (3H, m), 7.10-7.80 (14H, m), 8.20 (1H, d, J = 8Hz), 9.98 (1H, br s)

(5) (3RS)-1-(3,4-Diacetoxybenzyl)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one

(6) (3RS)-1-Benzyl-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one

mp : 145-150° C (dec.)
IR (Nujol) : 3250, 1680, 1635, 1600, 1530 cm^{-1}
NMR ($CDCl_3$, δ) : 4.88, 5.68 (2H, ABq, J = 15Hz), 5.93 (1H, d, J = 5Hz), 7.0-7.80 (19H, m), 8.25 (1H, d, J = 8Hz), 10.08 (1H, br s)
MASS : m/e = 484 (M^+)

benzodiazepine-2-one

mp : 125-130° C (dec.)
IR (Nujol) : 3250, 1680, 1630, 1600, 1535 cm^{-1}
NMR ($CDCl_3$, δ) : 2.45-2.85 (4H, m), 3.30-3.50 (2H, m), 3.50-3.90 (1H, m), 4.20-4.60 (1H, m), 5.80 (1H, d, J = 8Hz), 7.0-7.80 (14H, m), 8.25 (1H, d, J = 8Hz), 10.20 (1H, br s)

Example 23

A mixture of (3RS)-1-[2-(2-chloroethoxy)ethyl]-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (700 mg), potassium phthalimide (610 mg) and N,N-dimethylformamide (5 ml) was stirred for 7 hours at 80-90° C. The reaction mixture was poured into a cold water (100 ml) and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and evaporated to give (3RS)-1-[2-(2-phthalimidoethoxy)ethyl]-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (0.9 g).

Example 24

A mixture of (3RS)-1-[2-(2-chloroethoxy)ethyl]-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (500 mg) and 1-methylpiperazine (5.0 ml) was stirred at 70° C for 5.0 hours. Then diisopropyl ether (30 ml) was added to the reaction mixture. After the resultant precipitate was filtered off, the filtrate was evaporated. The residue was washed with water and dried to give (3RS)-1-[2-[2-(4-methyl-1-piperazinyl)ethoxy]ethyl]-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (0.43 g).
mp : 100-105° C (dec.)
IR (Nujol) : 3250, 1690, 1635, 1600, 1540 cm^{-1} NMR ($CDCl_3$, δ) : 2.15-2.60 (13H, m), 3.35-4.50 (6H, m), 5.80 (1H, d, J = 8Hz), 7.0-7.85 (14H, m), 8.15 (1H, d, J = 8Hz), 10.10 (1H, br s)
MASS : m/e = 564 (M^+)

Example 25

(1) A mixture of (3RS)-1-(2-phthalimidoethyl)-1,3- dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (1.04 g)and hydrazine hydrate (130 mg) in N,N-dimethylformamide (10 ml) was heated at 70° C under stirring for 3 hours. Additional hydrazine hydrate (130 mg) was added thereto. The resultant mixture was heated at 80° C for 12.5 hours. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and dried. The solvent was removed by evaporation under reduced pressure to afford a viscous oil (1.03 g), which was purified by column chromatography on silica gel with an eluent of a mixture of chloroform and methanol (50:1). The fractions containing the desired product were combined and evaporated to give (3RS)-1-(2-aminoethyl)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (0.76 g) as an amorphous oil, which was pulverized in ether by stirring. overnight to give crystalline powder (456.2 mg).
IR (Nujol) : 3260, 1690, 1660, 1620 cm^{-1}
NMR ($CDCl_3$, δ) : 3.3-3.8 (3H, m), 4.0-4.4 (1H, m), 5.83 (1H, d, J = 8Hz), 6.12 (2H, broad t), 7.1-7.9 (14H, m), 8.20 (1H, d, J = 8Hz), 9.85 (1H, broad s)

The following compound was obtained according to a similar manner to that of Example 25(1).

(2) (3RS)-1-[2-(2-Aminoethoxy)ethyl]-1,3-dihydro-3-(2-indolylcarbonylamino-5-phenyl-2H-1,4-benzodiazepine-2-one.

mp : 130-135° C (dec.)
IR (Nujol) : 3250, 1680, 1640, 1600, 1540 cm^{-1}
NMR ($CDCl_3$, δ) : 2.30-2.80 (2H, m), 3.0-4.0 (5H, m), 4.30-4.70 (1H, m), 5.80 (1H, s), 7.0-7.80 (14H, m)
MASS : m/e = 481 (M^+)

Example 26

IR (Nujol} : 3230, 1680, 1650, 1600, 1525 cm^{-1}
NMR (DMSO-d_6, δ) : 2.65-3.20 (2H, m), 4.30-4.90 (3H, m), 5.67 (1H, d, J = 8Hz), 7.0-7.80 (19H, m), 8.25-8.50 (1H, m), 9.37-9.57 (1H, m), 11.65 (1H, br s)
MASS : m/e = 598 (M^+)

Example 29

To a suspension of (3RS)-1-carboxymethyl-1,3-dihydro-3-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (1.53 g) in methylene chloride (30 ml) was added oxalyl chloride (1.29 g) under stirring and cooling in an ice-bath. The mixture was stirred for 3.5 hours at room temperature. The solvent and the excess oxalyl chloride were removed under reduced pressure and the residue was triturated in ether to give an acid chloride as an orange powder, which was collected by filtration, washed with ether and dried under reduced pressure. The powder (0.5 g) was added to a solution of cyanoamine (0.17 g) and triethylamine (0.42 g} in methylene chloride (20 ml) under stirring at room temperature. The mixture was stirred for 2 hours at the same temperature. To the reaction mixture was added methylene chloride (50 ml) and the mixture was washed with dilute hydrochloric acid and water. After being dried over magnesium sulfate, the organic layer was evaporated under reduced pressure. The residue was subjected to a column chromatography on silica gel with an eluent of a mixture of ethyl acetate, n-hexane and acetic acid (2:1:0.1) to give the desired product, which was stirred in ether to give (3RS)-1-[N-(cyano)carbamoylmethyl]-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one as a light orange powder (0.14 g).
mp : 255-260° C (dec.)
IR (Nujol) : 2170, 1680, 1640, 1600, 1540, 1460, 1380, 1305, 745 cm^{-1}
NMR (DMSO-d_6, δ) : 4.77 (2H, S), 5.75 (1H, d, J = 8Hz), 7.0-7.9 (14H, m), 9.52 (1H, d, J = 8Hz), 11.50 (1H, broad s)

Example 30

To a solution of (3RS)-1-(3-bromopropyl)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (0.52 g) in N,N-dimethylformamide (3 ml) was added methanolic sodium methanethiolate prepared from 30% methanolic methanethiol (0.48 g) and 1M methanolic sodium hydroxide (3.0 ml). The mixture was stirred for 6 hours and allowed to stand for 37 hours.

The reaction mixture was poured into water containing several drops of acetic acid under stirring and extracted with ethyl acetate twice, and the extracts were combined, washed with water three-times and dried over magnesium sulfate. The solvent was evaporated to dryness to afford yellow oil (0.59 g} which was subjected to column chromatography on silica gel with an eluent of a mixture of chloroform and ethyl acetate (20:1) to give a glassy material (330 mg). This material was stirred in diisopropyl ether overnight to give (3RS)-1-(3-methylthiopropyl)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (248.1 mg) as a white powder.
mp : 216-221° C
IR (Nujol) : 3430, 3260, 1673, 1638, 1600, 1532, 1450, 1375, 1270, 800, 778, 739, 695 cm^{-1}
NMR ($CDCl_3$, δ) : 1.7-2.0 (2H, m), 1.9 (3H, s), 2.25-2.45 (2H, m), 3.7-4.0 (1H, dt, J = 13.8Hz, 6.6Hz), 4.4-4.7 (1H, dt, J = 13.8Hz , 6.6Hz), 5.83 (1H; d, J = 7.8Hz), 7.1-7.8 (14H, m), 8.17 (1H, d, J = 7.8Hz), 10.01 (1H, br s)
MASS : m/e = 482 (M^+)

Example 31

(1) A mixture of (3RS)-1-(2-bromoethyl-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (501 mg), triethylamine (0.12 g), 4-mercarptopyridine (0.133 g) and N,N-dimethylformamide (6 ml) was stirred overnight at room temperature. The reaction mixture was poured into a mixture of water and ethyl acetate. The organic layer was separated, washed with water three times, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel with an eluent of ethyl acetate to give (3RS)-1-[2-(4-pyridylthio)ethyl]-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (0.19 g).
mp : 150-155° C (dec.)

to give an oil (19.30 g), which was chromatographed on silica gel with an eluent of a mixture of chloroform and methanol (30:1) to afford (3RS)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one (9.97 g).
NMR ($CDCl_3$, δ) : 2.42 (2H, broad s), 4.49 (1H, s), 5.06 (2H, s), 6.8-8.0 (25H, m)

Preparation 12

(1) To a solution of (3RS)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one (591.7 mg) in ethyl acetate (2 ml) was added a solution of (S)-(+)-mandelic acid (129.3 mg) in ethyl acetate (4 ml) under stirring at ambient temperature. The precipitated gel was dissolved by addition of methanol (0.2 ml). To the clear solution were added ethyl acetate (4 ml) and diisopropyl ether (three drops). The mixture was stirred for 2 hours and allowed to stand overnight. The resultant precipitates were collected by filtration, washed with ethyl acetate and diisopropyl ether and dried to give white powder (202.2 mg), which was recrystallized from ethyl acetate to afford (S)-(+)-mandelic acid salt of (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one as crystals.
$[\alpha]_D^{24}$ = -33.33° (C = 0.846, CH_3OH)

Further, a mixture of (3R)-1,3-dihydro-5-(-2fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one and (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one was obtained from the filtrate.

(2) (S)-(+)-Mandelic acid salt of (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trytyl-4-imidazolyl)-methyl-2H-1,4-benzodiazepine-2-one obtained in Preparation 12(1) was suspended in a mixture of water and ethyl acetate. The resultant mixture was adjusted to pH 7-8 with an aqueous solution of sodium bicarbonate under stirring. The organic layer was separated, washed with water and evaporated to dryness to give (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one (181.4 mg).
$[\alpha]_D^{24}$ = -35.34° (C = 0.846, CH_3OH)

Preparation 13

(1) A mixture ($[\alpha]_D$ = +14.4°) (1.57 g) of (3R)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one and (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one obtained in Preparation 12(1) was dissolved in a mixture of ethyl acetate (5.3 ml) and methanol (0.5 ml). To a solution was added a solution of (R)-(-)-mandelic acid (342.7 mg) in ethyl acetate (20 ml) under stirring at ambient temperature. To the mixture was added diisopropyl ether (0.5 ml) and the resultant mixture was stirred for 2 hours and allowed to stand overnight. The precipitates were collected by filtration, washed with ethyl acetate and diisopropyl ether and dried to give (R)-(-)-mandelic acid salt of (3R)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one (white powder, 685.6 mg).
$[\alpha]_D^{24}$ = +33.60° (C = 0.848, CH_3OH)

(2) (3R)-1,3-Dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one was obtained by treating (R)-(-)-mandelic acid salt of 3R)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one in a similar manner to that of Preparation 12(2).
$[\alpha]_D^{22}$ = +37.91° (C = 0.844, CH_3OH)

Example 33

The following compounds were obtained according to a similar manner to that of Example 6(1).

(1) (3S)-1,3-Dihydro-1-(1-trityl-4-imidazolyl)methyl-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

NMR ($CDCl_3$, δ) : 5.085 (2H, ABq), 5.76 (1H, d, J = 7.9Hz), 6.8-8.0 (30H, m), 8.10 (1H, d, J = 7.9Hz), 9.81 (1H, s)

(12) (3S)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one hydrochloride

NMR (DMSO-d_6, δ) : 5.33 (2H, ABq), 5.69 (1H, d, J = 7.6Hz), 7.0-8.0 (15H, m), 9.05 (1H, s), 9.60 (1H, d, J = 7.6Hz), 11.74 (1H, s), 14.73 (1H, broad s)

Example 34

A mixture of (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one (0.79 g), indole-2-carboxylic acid g), N-hydroxybenzotriazole (0.18 g) and N,N'-dicyclohexylcarbodiimide. (0.28 g) in N,N-dimethylformamide (8 ml) was stirred at ambient temperature overnight and filtered. The filtrate and washincs were diluted with ethyl acetate. The mixture was washed with an aqueous solution of sodium bicarbonate. The separated organic layer was washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure to give a viscous oil (1.12 g), which was chromatographed on silica gel with an eluent of a mixture of chloroform and methanol (30:1) to afford (3S)-1,3-dihydro-1-(1-trityl-4-imidazolyl)methyl-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (amorphous substance, 0.97 g).
$[\alpha]_D^{23}$ = -32.47° (C = 0.85, CH_3OH)
NMR ($CDCl_3$, δ) : 5.085 (2H, ABq), 5.76 (1H, d, J = 7.9Hz), 6.8-8.0 (30H, m), 8.10 (1H, d, J = 7.9Hz), 9.81 (1H, s)

Example 35

To a solution of (3R)-1,3-dihydro-1-(1-trityl-4-imidazolyl)methyl-3-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (0.81 g), indole-2-carboxylic acid (0.23 g), N-hydroxybenzotriazole (0.19 g) in N,N-dimethylformamide (8 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.27 g) and triethylamine (0.14 g) under stirring at ambient temperature. The mixture was stirred for 4 hours at ambient temperature. To the reaction mixture were added ethyl acetate and water under stirring. The mixture was adjusted to pH 8 with an aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The separated organic layer and the extract were combined, washed with water twice and dried over magnesium sulfate. The solvent was removed under reduced pressure to give (3R)-1,3-dihydro-1-(1-trityl-4-imidazolyl)methyl-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (1.0 g).
$[\alpha]_D^{22}$ = +41.58° (C = 0.856, CH_3OH) NMR (DMSO-d_6, δ) : 5.11 (2H, ABq), 5.64 (1H, d, J = 8.0Hz), 6.7-8.0 (30H, m), 9.55 (1H, d, J = 8.0Hz), 11.66 (1H, s)

Example 36

To a solution of (3S)-1,3-dihydro-1-(1-trityl-4-imidazolyl)methyl-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (1.0 g) in N,N-dimethylformamide (10 ml) was added 6N hydrochloric acid (7 ml) under stirring and cooling in an ice-bath. The mixture was warmed to 50° C and stirred for 2 hours. After cooling to room temperature, to the reaction mixture were added water and ethyl acetate under stirring. The mixture was adjusted to pH 8 with an aqueous solution of sodium bicarbonate. The separated organic layer was washed with water and dried. Removal of the solvent gave a viscous oil (1.20 g), which was chromatographed on silica gel with an eluent of a mixture of chloroform and methanol (20:1) to afford (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (601.5 mg) as an yellow crystalline powder.
$[\alpha]_D^{20}$ = +24.68° (C = 0.64, $CHCl_3$)
NMR (DMSO-d_6, δ) : 5.04 (2H, ABq), 5.63 (1H, d, J = 7.9Hz), 6.9-8.2 (15H, m), 9.58 (1H, d, J = 7.9Hz), 11.65 (1H, s), 11.92 (1H, s)

Example 37

The following compound was obtained according to a similar manner to that of Example 36.

(2) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(4-imidazolylmethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

NMR ($CDCl_3$, δ) : 4.85, 5.10 (2H, ABq, J = 15Hz), 5.80 (1H, d, J = 8Hz), 6.80-7.83 (15H, m), 8.10 (1H, d, J = 8Hz), 10.10 (1H, broad s)

(3) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-[(5-methylimidazol-4-yl)methyl]-5-phenyl-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ) : 1.96 (3H, s), 4.80, 5.15 (2H, ABq, J = 15Hz), 5.55 (1H, d, J = 8Hz), 6.90-8.15 (15H, m), 9.33 (1H, d, J = 8Hz), 11.58 (2H, br s)

(4) (3S)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ) : 5.04 (2H, ABq), 5.63 (1H, d, J = 7.9Hz), 6.9-8.2 (15H, m), 9.58 (1H, d, J = 7.9Hz), 11.65 (1H, s), 11.92 (1H, s)

(5) (3R)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ) : 5.04 (2H, ABq), 5.62 (1H, d, J = 7.9Hz), 6.9-8.3 (15H, m), 9.58 (1H, d, J = 7.9Hz), 11.66 (1H, s), 11.93 (1H, s)

(6) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(2-imidazolylmethyl)-5-phenyl-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ) : 5.10 (2H, s), 5.65 (1H, d, J = 8Hz), 6.60-8.10 (16H,. m), 9.36 (1H, d, J = 8Hz), 11.65 (1H, br s), 11.90 (1H, br s)

(7) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(3-pyrazolylmethyl)-5-phenyl-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ) : 5.03, 5.30 (2H, ABq, J = 15Hz), 5.65 (1H, d, J = 8Hz), 5.85 (1H, br s), 6.90-7.90 (15H, m), 9.43 (1H, d, J = 8Hz), 11.60 (1H, br s), 12.55 (1H, br s)

(8) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-[(1,2,4-triazol-3-yl)methyl]-5-phenyl-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ) : 5.10, 5.35 (2H, ABq, J = 15Hz), 5.66 (1h, d, J = 8Hz), 6.90-7.93 (15H, m), 8.23 (1H, br s), 9.40 (1H, d, J = 8Hz), 11.65 (1H, br s)

(9) (3RS)-1,3-Dihydro-3-(2_indolylcarbonylamino)-1-[2-(4-imidazolyl)ethyl]-5-phenyl-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ) : 2.63 (2H, t, J = 7Hz), 3.85-4.20 (1H, m), 4.20-4.75 (1H, m), 5.55 (1H, d, J = 8Hz), 6.60 (1H, s), 6.93-7.85 (15H, m), 9.43 (1H, d, J = 8Hz), 11.65 (1H, br s)

(10) (3S)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamio)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one hydrochloride

NMR (DMSO-d_6, δ) : 5.33 (2H, ABq), 5.69 (1H, d, J = 7.6Hz), 7.0-8.0 (15H, m), 9.05 (1H, s), 9.60 (1H, d, J = 7.6Hz), 11.74 (1H, s), 14.73 (1H, broad s)

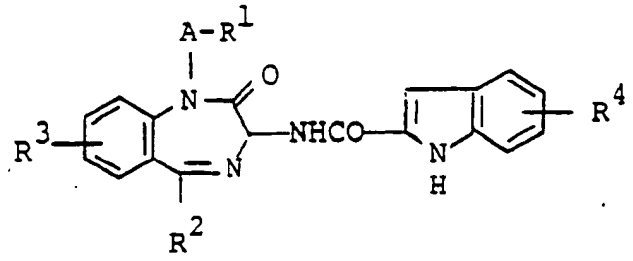
Claims

1. A compound of the formula : .

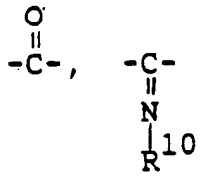
A is C_1-C_3 alkylene.

6. A compeund of claim 5,
which is (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one.

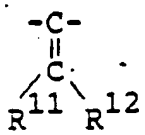
7. A process for preparing a compound of the formula :



wherein R^1 is halogen,
heterocyclic group which may have one or more suitable substituent(s), aryl which may have one or more suitable substituent(s),
-NH-R^5 (in which R^5 is hydrogen, lower alkanoyl or hydroxy(lower)alkyl),
-S-R^6 (in which R^6 is lower alkyl, lower alkyl substituted with carboxy and amino, lower alkyl substituted with protected carboxy and protected amino, or pyridyl),
-O-R^7 (in which R^7 is hydrogen, hydroxy protective group, lower alkyl, lower alkenyl, ar(lower)alkyl, halo(lower)alkyl, amino(lower)alkyl, protected amino(lower)alkyl, or piperazinyl(lower)alkyl which may have lower alkyl),
-CONH-R^8 (in which R^8 is cyano, carbamoyl(lower)alkyl, carboxy(lower)alkyl, protected carboxy(lower)alkyl, or lower alkyl substit7uted with carbamoyl and aryl), or
-Z-R^9 [in which R^9 is hydrogen or lower alkyl, and Z is

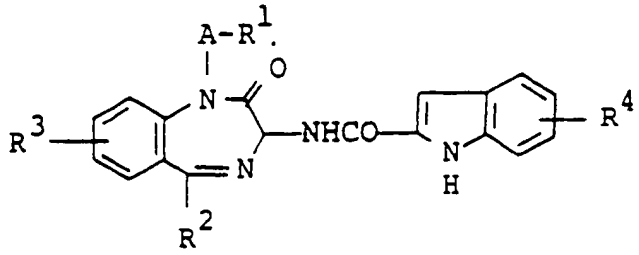


(wherein R^{10} is hydroxy, lower alkoxy or amino) or



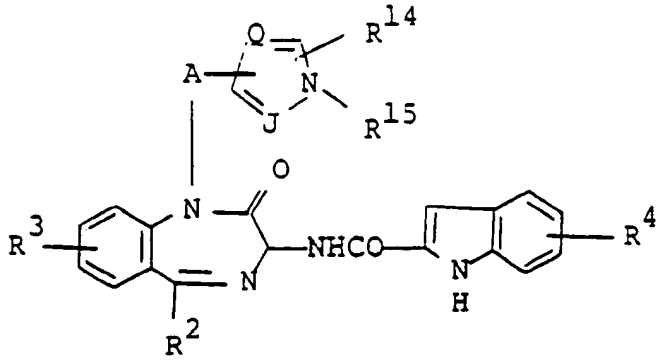
(wherein R^{11} is carboxy or protected carboxy and R^{12} is hydrogen; or
R^{11} is halogen and R^{12} is halogen)],
R^2 is aryl which may have one or more suitable substituent(s),
R^3 is hydrogen or halogen,
R^4 is hydrogen, halogen or lower alkoxy and
A is lower alkylene,
or a salt thereof,
which comprises

(1) reacting a compound of the formula :

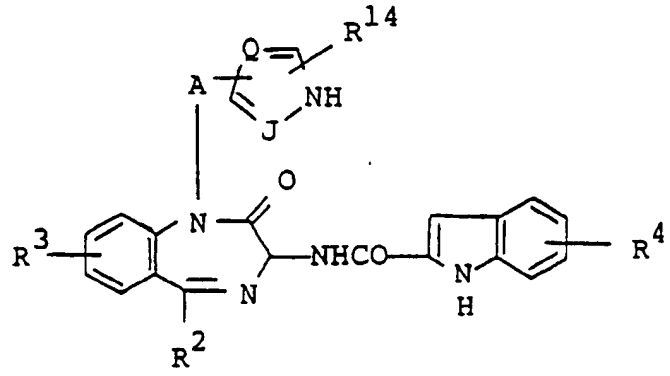


wherein R^1, R^2, R^3, R^4 and A are each as defined above,
or a salt thereof, or

(3) subjecting a compound of the formula :



wherein R^2, R^3, R^4 and A are each as defined above,
R^{14} is hydrogen or lower alkyl,
R^{15} is an imino protective group,
J is CH or N and
Q is CH or N,
or a salt thereof to elimination reaction of the imino protective group to give a compound of the formula :



wherein R^2, R^3, R^4, R^{14}, A, J and Q are each as defined above,
or a salt thereof.

8. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

9. A compound of claim 1 or pharmaceutical acceptable salt thereof for use as a medicament.

10. A compound of claim 1 or pharmaceutical acceptable salt thereof for use as a cholecystokinin antagonist.

11. A compound of claim 1 or pharmaceutical acceptable salt thereof for use in treating or preventing emesis or pancreatitis.

12. Use of a compound of claim 1 or pharmaceutical acceptable salt thereof for the manufacture of a medicament for therapeutic treatment of emesis or pancreatitis.

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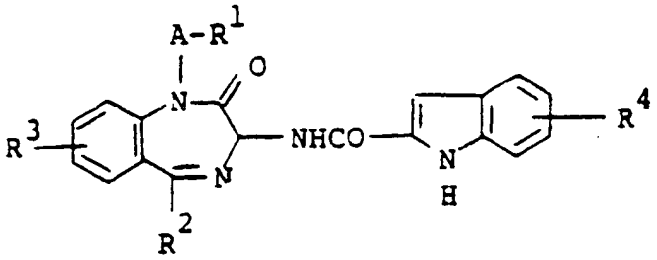
(54) Benzodiazepine derivatives.

(57) A compound of the formula :



wherein R^1 is halogen,
heterocyclic group which may have one or more suitable substituent(s), aryl which may have one or more suitable substituent(s),
-NH-R^5 (in which R^5 is hydrogen, lower alkanoyl or hydroxy(lower)alkyl),
-S-R^6 (in which R^6 is lower alkyl, lower alkyl substituted with carboxy and amino, lower alkyl substituted with protected carboxy and protected amino, or pyridyl),
-O-R^7 (in which R^7 is hydrogen, hydroxy protective group, lower alkyl, lower alkenyl, ar(lower)alkyl, halo(lower)-alkyl, amino(loweralkyl, protected amino(lower)alkyl, or piperazinyl(lower)alkyl which may have lower alkyl),
-CONH-R^8 (in which R^8 is cyano, carbamoyl(lower)alkyl, carboxy(lower)alkyl, protected carboxy(lower)alkyl, or

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EUROPEAN SEARCH REPORT

Application Number

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 167 919 (MERCK & CO. INC.)		C 07 K 5/06 A 61 K 37/02 A 61 K 37/43
A	PROC. NATL. ACAD. SCI. USA, vol. 83, July 1986, pages 4923-4926; R.S.L. CHANG et al.: "Biochemical and pharmacological characterization of an extremely potent and selective nonpeptide cholecystokinin antagonist"		

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 K
A 61 K
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The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	10 June 91	DEFFNER C-A.E.

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